AMENDMENTS TO THE DRAWINGS

Please replace the original drawing sheets containing Figures 3-6 with the attachment sheets of corrected drawings, Figures 3-6.

REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

I. CLAIM STATUS & AMENDMENTS

Claims 1-21, 26 and 27 were pending in this application when last examined and stand rejected.

Claim 1 is amended to incorporate the subject matter of claims 2, 7 and 10 and to further define the residues of R^b, R^c, R^d, and R^R as supported by the disclosure and the examples, for instance, at page 28, Table 2.

Claim 1 is further amended to replace "low" with "less than 20%" in relation to binding affinity. Support can be found in the disclosure, for example, at at page 12, lines 23-25 and original claim 2.

Support for the amendment to claim 2 can be found in the claim as filed.

Claims 8, 12, and 14 are amended to change their dependency from claim 7 (now cancelled) to claim 1.

Other editorial changes were made to better conform to US practice and English grammar form. See for instance, the revisions to claims 15-18. Such amendments are editorial and non-substantive. They are not intended to narrow the scope of protection.

No new matter has been added by the above claim amendments.

Claims 7, 9, 10, and 27 are cancelled without prejudice or disclaimer thereto. Applicants reserve the right to file a continuation or divisional on any canceled subject matter.

Claims 1-6, 8, 11-21 and 26 are pending upon entry of this amendment.

A revised substitute Abstract is enclosed herewith to replace the original Abstract. Editorial and formatting revisions were made to the Abstract to better conform to US practice. Support can be found in the original Abstract and the claims as filed. No new matter has been added.

Replacement drawings (Figures 3-6) are attached herewith to replace Figures 3-4. Support can be found in the drawings as filed and the Brief Description of the drawings. No new matter has been added.

II. OBJECTIONS TO THE ABSTRACT & DRAWINGS

The Abstract and the drawings were objected to for the reasons set forth on page 2 of the Office Action.

It is respectfully submitted that the present amendment overcomes these objections.

First, the revised Abstract better conforms to US practice and format.

Second, the revised Figures 3-6 clearly indicate what parameters are plotted in the X and Y axes based on the Brief Description of the drawings.

Thus, the above-noted objections are untenable and should be withdrawn.

III. ENABLEMENT REJECTION

Claims 20 and 21 were rejected under 35 U.S.C. § 112, first paragraph, on the basis that the specification is enabling for the treatment and diagnosis of cancer, but not for the treatment and diagnosis of infection by microorganisms.

This rejection is respectfully traversed as applied to the amended claims.

First, enclosed herewith is a copy of a publication which confirms that a compound of the invention accumulates in microorganisms causing infection. This poster was presented at the 4th Swiss Experimental Surgery Symposium (January 10-11, 2008, Geneva, Switzerland). Compound PAMA-4 shown in figure 1 of the poster is the compound of Example 13 complexed with ^{99m}Tc. Reference to this symposium may be found in the internet: **www.sess08.medicine.uinge.ch**. Accordingly, it is respectfully submitted that the skilled artisan, upon reading such, would clearly believe that the instant application is useful in a method of diagnosis of a neoplastic disease or an infection by microorganisms in a mammal, as well as a method of treating such.

Second, Applicants herein provide comments on the Examiner's positions as set forth in the Office Action.

As to the breadth of the claims: The prediction made at the time of filing due to the distribution of compounds of the invention when injected into mice fed with vitamin B12 deficient food was that such compounds should accumulate in non-normal cells in the animal body, either tumor cells or foreign organisms, e.g. microorganism. It is respectfully submitted that an exemplification of particular cases is not needed.

As to the state of the prior art: The Office relied on Morgan et al. (WO 95/27723) as evidence of the state of the art. It was indicated that Morgan, that is directed to cobalamin derivatives, discloses the use of such derivatives for the treatment of cancer, but is silent regarding the diagnosis and treatment of infections by microorganisms.

In reply, it is noted that Morgan was looking for vitamin B12 derivatives binding to TC II, see e.g. page 3 (background section), figures 22-25, and page 12, line 26 to page 13, line 5.

By contrast, the Applicants have made the observation that particular useful vitamin B12 derivatives of the present invention are those that do not bind to TCII, and concluded that such compounds are much better in their ability to be accumulated in tumor cells and microorganisms.

Also, based on the disclosure in the instant specification, it is clear that the cobalamin derivatives of the present invention can be used to carry therapeutic and/or diagnostic agents. In this regard, it is clear that the cobalamin derivatives of the present invention exhibit a much reduced accumulation in blood and normal tissues, but have high uptake rates in hyperproliferative. Accordingly, one skilled in the art, upon reading this disclosure and in view of the knowledge in the art, would reasonably believe that the instant invention enables a more precise diagnosis and therapy of neoplastic diseases and local infections. See for instance, the disclosure at page 4-5 and page 7.

Regarding the level of predictability in the art: There is no doubt that there are several types of infections by microorganisms. However, since the vitamin B12 derivatives of the invention share the common property of accumulating in microorganisms (in comparison to accumulation in organs of the mammal treated), their usefulness for treating infections is neither dependent on the particular type of infection nor the particular microorganism.

Regarding the amount of direction in the disclosure: At page 4 of the Action, the Examiner indicated that the specification (at page 6) just recites that the instant compounds are of high value in the treatment and diagnosis of infections by pathogenic microorganisms. In reply, it is respectfully submitted that the one skilled in the art would not find the guidance on page 6 of the disclosure to be insufficient or wrong. Contrary to the Office's position, Applicants are correct in their conclusion that the vitamin B12 derivatives of the invention are useful for treating infections.

The existence of working examples: It is well established that compliance with the enablement requirement of 35 USC 112, first paragraph, does not turn on whether an example is disclosed. An

example may be "working" or "prophetic." There is no statutory requirement for working examples. Though lack of a working example is a factor to be considered, if all the other factors point toward enablement, then the absence of working examples will not by itself render the invention non-enabled. See MPEP 2164.02. It is respectfully submitted that all other factors point toward enablement for the reasons discussed herein.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: It is respectfully submitted that no further experimentation is needed to confirm that the vitamin B12 derivatives of the invention not only accumulate in tumor cells, but also in microorganism.

Therefore, it is clear that the cobalamin derivatives of the present invention exhibit a much reduced accumulation in blood and normal tissues, but have high uptake rates in hyperproliferative, and that they can be used to carry diagnostic reagents and therapeutic agents. As such, one skilled in the art, upon reading this disclosure and in view of the knowledge in the art, would reasonably believe that the instant invention enables a more precise diagnosis and therapy of neoplastic diseases and local infections.

Therefore, the above-noted enablement rejection is untenable and should be withdrawn.

IV. INDEFINITENESS REJECTION

Claims 1-21 and 26-27 were rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the reasons set forth on page 5 of the Office Action.

It is respectfully submitted that the present amendment overcomes this rejection.

First, claim 1 has been amended to replace "low" with "less than 20%" in relation to binding affinity as supported by the disclosure at page 12, lines 23-25. See also the language of original claim 2.

Second, for the sole purpose of expediting prosecution and not to acquiesce to the rejection, claim 27 has been cancelled, thereby obviating the Examiner's concern for claim 27.

Therefore, the above-noted indefiniteness rejections are untenable and should be withdrawn.

V. ANTICIPATION REJECTION

On page 6 of the Office Action, claims 1-5, 7-9, 12-13, 19, 21 and 27 were rejected under 35 U.S.C. § 102(b) as anticipated by Morgan et al. (WO 95/27723).

It is respectfully submitted that the present amendment overcomes this rejection.

To anticipate a claim, a cited prior art reference must disclose each and every element of the claim.

Applicants respectfully submit that Morgan fails to disclose or suggest each and every element of amended independent claim 1.

First, claim 1 has been amended to incorporate the subject matter of claim 10, which was not included in this rejection. For this reason alone, the rejection is untenable and should be withdrawn.

Second, claim 1 is amended define that at least one of the residues of R^b, R^c, R^d, and R^R is a spacer-chelator of a specifically defined group. Morgan fails to disclose or suggest this aspect of the claimed invention. The compounds of Morgan et al., Figure 8, wherein R_2 is GABA or GABA-peptide or peptide do not fall under the scope of amended claim 1. Neither GABA, GABA-peptide nor a peptide are a spacer-chelator group as now required in amended independent claim 1. The compounds of Morgan comprising cobalamin and acridine, chloroquine and quinacridine dyes likewise do not fall under the scope of amended claim 1. None of the dyes attached to the cobalamin in Morgan is a spacer-chelator group as now required by amended claim 1.

Thus, amended claim 1 now incorporates the subject matter of non-rejected claim 10 and claim 1 does not comprise the compounds as disclosed by Morgan. Accordingly, Morgan fails to disclose each and every element of the claimed invention. Therefore, the present invention of independent is novel and patenable over Morgan.

Since the remaining claims directly or indirectly depend on claim 1, they are also novel and patentable over Morgan for the same reasons set forth above regarding claim 1.

Therefore, the above-noted anticipation rejection over Morgan is untenable and should be withdrawn.

VI. OBVIOUSNESS REJECTION

On page 8 of the Office Action, claims 6-7, 10-12, 14-18, 20 and 26 were rejected under 35 U.S.C. § 103(a) as obvious over Morgan et al. (WO 95/277723) and Grissom et al. (U.S. 6,797,521) in view of Collins (U.S. 5,739,313).

This rejection is respectfully traversed as applied to the amended claims.

The arguments with respect to the primary reference, Morgan, are reiterated herein. Namely, Morgan fails to disclose or suggest the subject matter of claim 10 (now incorporated in independent claim 1) and the definition of the residues of R^b, R^c, R^d, and R^R of the spacer-chelator of the specifically defined group.

It is respectfully submitted that the secondary references, Grissom and Collins< fail to remedy the deficiencies in Morgan. Consequently, the combination of Morgan, Grissom and Collins fails to disclose each and every element of the claimed invention.

In this regard, and as explained above, Morgan was looking for vitamin B12 derivatives binding to TC II. Accordingly, based on disclosure in Morgan, it is not at all obvious that particularly useful vitamin B12 derivatives are those that do not bind to TCII, and that such compounds have a substantially improved selectivity for accumulation in tumor cells and microorganisms. Thus, there is clearly no suggestion in Morgan for this aspect of the present invention.

None of the secondary references give any indication that, contrary to the general opinion, a vitamin B12 derivative being a TCII non-binder should be used for the treatment of tumors and infections by microorganisms.

Grissom discloses fluorescent cobalamin useful in the diagnosis of cancer cells.

Collins describes chelating vitamin B12 derivatives further comprising a detectable radionuclide or paramagnetic metal ion, but both references are silent whether there are particular aspects important for cancer treatment and treatment of infection by microorganisms, such as binding to TCII.

Thus, it is respectfully submitted that the cited references lack a suggestion that the particularly useful vitamin B12 derivatives of the present invention are those that do not bind to TCII and that such compounds have a substantially improved selectivity for accumulation in tumor cells and microorganisms. Consequently, one of ordinary skill in the art, upon reading the cited references, would not arrive at the present invention. For this reason, the present invention

is novel and unobvious over the combined references. Thus, the above-noted obviousness rejection is untenable and should be withdrawn.

VII. CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

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January 31, 2008

ATTACHMENTS

1. Copy of a publication which confirms that a compound of the invention accumulates in microorganisms causing infection. This poster was presented at the 4th Swiss Experimental Surgery Symposium (January 10-11, 2008, Geneva, Switzerland).
2. Replacement drawings for Figures 3-6.

POTENTIALS OF RADIOLABELED VITAMIN B12 DERIVATIVES FOR DIAGNOSIS OF IMPLANT INFECTION

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Introduction

Implants are increasingly used in modern medicine to replace missing function or anatomic structure. Implant **infection** is the most devastating complication, caused by bacteria growing on the implant surface as **biofilms**.

An accurate diagnosis of **infection** is crucial for successful treatment. Standard diagnostic methods are slow (culture), invasive (surgery) and lack sensitivity. Preoperative imaging is an attractive non-invasive approach, but current techniques (scintigraphy) lack specificity. A selective tracer is needed for accurate discrimination of infection from sterile inflammation.

Vitamin B_{12} (cobalamin) is a promising candidate for imaging infections due to its high requirement in proliferating cells. Recently, cobalamin derivatives with reduced accumulation in eukaryotic cells (transcobalamin II non-binders) have been developed to increase discriminative ability for infections/tumors and decrease systemic toxicity. ^{99m}Tc has a half-life of 6 h and energy of 140 keV, which is sufficient to penetrate human tissue without much attenuation and thus can be externally monitored by a gama-camera. We assessed a ^{99m}Tc-labeled cobalamin derivative PAMA-4 (**Figure 1**) for imaging of infections in a mouse model of implant infection.

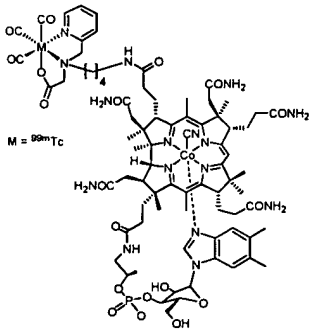

Figure 1. ^{99m}Tc labeled cobalamin derivative PAMA-4.

Methods

Animals. C57BL/6 mice, aged 12–16 weeks, were put on vitamin B_{12}-free diet for 3 weeks. A sterile Teflon cage was subcutaneously implanted in the mice back. Two weeks after implantation, mice were randomly assigned to 3 groups for percutaneous injection into the cage:

- Infection (n = 6): ≈10^4 CFU *Staphylococcus aureus* (ATCC 35556). Bacterial count in the cage was assessed 24 h after infection by quantitative culture of aspirated cage-fluid.
- Sterile inflammation (n = 2): 10 µg lipopolysaccharide (LPS). The polymorhonuclear leukocytes (PMN) number in the cage fluid was determined up to 72 h. Cells were stained with Turk's solution and counted in a Neubauer chamber.
- No inflammation (n = 4): saline

Imaging. 24 h after infection, ^{99m}Tc-PAMA-4 (240-440 MBq) was injected either intravenously or directly in the cage, followed by SPECT/CT imaging 24 h and 48 h later. Shortly before imaging, mice were scarified by thiopental injection i.p.

Results

Infection and sterile inflammation. After infection the bacterial count in cage fluid ranged between 5 x 10^5 and 9 x 10^6 CFU/ml. Sterile inflammation was confirmed and quantified by the increase in PMN counts in cage fluid over 72 h (**Table 1**).

	24 h	48 h	72 h
PMN_t/PMN_0	1.5	3.0	3.0

Table 1. PMNt/PMN0 in cage fluid calculated from PMN counts before (PMN_0) and 24 h, 48 h and 72 h after LPS injection (PMN_t).

Intravenous injection of PAMA-4. SPECT/CT imaging showed no significant accumulation of the tracer in both infected and sterile cages.

Injection directly of PAMA-4 in the cage. The 24 h scan showed equal retention of the tracer in infected and control mice. Imaging after 48 h showed selective retention of the tracer in infected cages compared to sterile controls with and without inflammation (**Figure 2**).

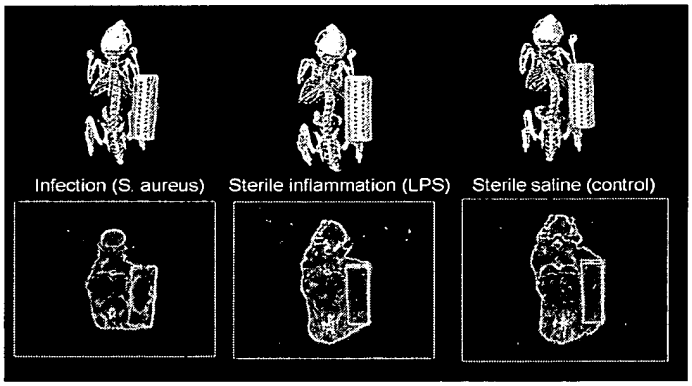

Figure 2. SPECT/CT imaging 48 h after in-cage injection of PAMA-4. The cage was either infected with *S. aureus* (left), induced sterile inflammation by lipopolysaccharide (middle) or without inflammation (right).

Conclusions

Radiolabeled cobalamin derivative PAMA-4 is a promising candidate for imaging infections by SPECT/CT, discriminating well between infection and sterile inflammation after injection into the cage.

No accumulation of the tracer was observed after intravenous administration, which may reflect its short biological half-life or limited penetration in the cage.

Further studies are needed to evaluate the value of radiolabeled cobalamin derivatives for imaging infections.

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